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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/155,676	01/04/99	WALLACH D	WALLACH=21

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EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	12

DATE MAILED: 04/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/155,676	David Wallach et al.
Examiner	**Group Art Unit**
Janet Epps	1635

☒ Responsive to communication(s) filed on *Feb 4, 2000*

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *13-16 and 20-60* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *13-16 and 20-60* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of the invention of Group II, claim(s) 17-21, and 43-49, drawn to a TRAF-binding protein encoded by said DNA, isoforms, fragments, analogs and derivatives thereof; method for their production and methods for screening a ligand capable of binding to said protein, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the claimed proteins do not read on the proteins known in the art, and that the inventions do relate to a single general inventive concept. Applicant's amendment to the claims of the instant application overcomes the prior art that read on claims 1-4 of the originally filed claims. The inventions of Groups I-IV no longer lack the same or corresponding technical features. The special technical feature shared among the inventions of the present application appears to be a protein which binds to a TRAF2 protein and modulates the activity of NF-kb having the amino acid sequence as described in claim 1 of the instant application. The prior art does not teach the claimed amino acid sequence, therefore all claims will be examined as a single invention.

Sequence Information

2. The sequence listing for this application is technically sound and has been entered into the Sequence Database of the USPTO.

Art of Interest (Not prior art)

3. The Examiner would like to draw Applicant's attention to US Patents 5,843,721 and 5,844,073. The cited patents were both issued on December 1, 1998, and have a filing date of July 3, 1997.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 22, 26-29, 31-39, 53, 55 and 58-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites "[a]ntibodies ....or derivative thereof according to claim 19 or 20". There is lack of antecedent basis of these limitations in claim 19 since claim 19 is a canceled claim. Furthermore, by convention there should be only one invention recited per claim. Since this claim reads on multiple "[a]ntibodies or fragments or derivatives thereof...", there is ambiguity as to whether the claim reads on one particular antibody or several different antibodies. Applicants are invited to amend the first line of this claim to read "An antibody or derivative thereof' in order to obviate this rejection.

Claims 26-28 recite "TRAF2 modulated/mediated effect on cells" this phrase is vague and indefinite since the metes and bounds of the meaning of this phrase is unclear.

Claims 27 and 29 recite the phrase "the TRAF2 modulated/mediated effect on cells", there is lack of antecedent basis for this limitation in these claims.

Claim 31 recites the phrase "[a] method according to claim 23 wherein said protein is NIK or at least one of the NIK isoforms, analogs, fragments and derivatives thereof." There is lack of antecedent basis for these limitations in claim 23.

Claim 53 recites "[a] polypeptide in accordance with claim 51, wherein said polypeptide of (a) is NIK (SEQ ID NO:7)". There is lack of antecedent basis for this limitation in claim 51 since there is no direct reference to the NIK polypeptide in claim 51.

Claim 55 recites the phrase "moderately stringent conditions", this phrase is vague and indefinite since the metes and bounds of the term "moderately" in this context is uncertain.

Claim 58 recites "[a] DNA sequence in accordance with claim 55, comprising a DNA sequence encoding the protein NIK or SEQ ID NO:7." This claim is vague and indefinite since claim 55 recites a variety of DNA sequences of different composition and length, it is unclear how the variety of sequences recited in claim 55 can all encode the same proteins.

Claim 59 recites "[a] DNA sequence encoding ...(2) a DNA sequence", this phrase is vague and indefinite since it is obvious that a DNA sequence does not encode a DNA sequence.

Claim 60 recites "said anti-sense oligonucleotide being capable of effectively blocking the translation of said mRNA." The term "capable" as used in this phrase is vague and indefinite since it suggests latent function of the anti-sense oligonucleotide which may or may not be functional under certain conditions.

6. Claims 32-39 provide for the use of a pharmaceutical composition, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 32-39 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 13-16, 20-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 51 and those dependent therefrom read on a polypeptide that binds to TRAF2 and modulates the activity of NF-kB, said polypeptide comprising the amino acid sequence of a fragment, analog or derivative of the amino acid sequence of SEQ ID NO:2, an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:3, or the amino acid sequence of SEQ ID NO:5,

polypeptide analogs of said fragments, and polypeptide derivatives of said analogs, wherein said polypeptides bind to TRAF2 and modulates the activity of NF-kB.

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus of fragments, analogs , and derivatives the polypeptides and polypeptide analogs recited in claim 51 of the instant application. The analogs comprise an amino acid sequence having no more than ten changes in the amino acid sequence of amino acid sequence of SEQ ID NO:2, an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:3, or the amino acid sequence of SEQ ID NO:5, or fragments of these amino acid sequences. The specification as filed states "suitable fragments of TRAF-binding proteins are those which retain the TRAF-binding protein capability and which can mediate the biological activity of TRAF proteins to other proteins associated with TRAF proteins directly or indirectly (p. 28, lines 2-4)" , and defines "derivatives as used herein covers derivatives which may be prepared from the functional groups which occur as side chains on the residues or the N- or C-terminal groups, by means known in the art"(p.28, lines 16-18). Although the specification as filed teaches that derivatives, fragments, and analogs are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made in order to isolate the recited fragments of the claims polypeptides, analogs of said polypeptides and fragments, and derivatives of said polypeptides which retain the ability to bind TRAF2 and modulate the activity of NF-kB. Structural features that could distinguish compounds in the genus from others in the polypeptide class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not

supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the recites amino acid sequences of SEQ ID NO:2, and 5, and the amino acid encoded by the nucleotide sequence of SEQ ID NO: 3, alone is not sufficient to describe claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

9. Claim 55 and those dependent therefrom read on a DNA sequence encoding a polypeptide that binds to TRAF2 and modulates activity of NF-kB, selected from the group consisting of a DNA sequence capable of hybridization under moderately stringent conditions to a sequence of the cDNA of SEQ ID NO:1, 3, 4, or fragments of those sequences which encode a polypeptide that binds to TRAF2 and modulates the activity of NF-kB.

One of ordinary skill in the art would reasonably conclude that hybridization under moderately stringent conditions may result in hybridization to nucleic acid sequences beyond the description of nucleic acid sequences provided in the instant application. Thus, applicant was not in possession of the claimed genus.

10. Claims 27-29, 34, 40-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 27-29, and 34 read on pharmaceutical compositions comprising an oligonucleotide encoding an anti-sense sequence of the mRNA encoding a polypeptide according to claim 51, and methods for modulating the TRAF2 modulated/mediated effect on cells comprising treating said cells with an oligonucleotide encoding an antisense sequence for at least part of the DNA sequence encoding a polypeptide according to claim 51, or a ribozyme capable of interacting with a cellular mRNA sequence encoding a polypeptide according to claim 51.

In regards to the claimed methods of modulating the TRAF2 modulated/mediated effect on cells and the pharmaceutical composition comprising an antisense oligonucleotide, the claimed methods and composition read on *in vivo* applicability for enablement purposes. The specification as filed does not provide sufficient instruction, guidance and/or description describing a sufficient number of examples wherein applicants have successfully demonstrated that the claimed methods and compositions are effective in modulating the TRAF2 modulated/mediated effect on cells either *in vitro* or *in vivo*. In addition the target of the antisense or ribozyme used in the recited methods is extremely broad. The polypeptide recited in claim 51 of the instant application, reads on analogs, and derivatives of the amino acid sequence of SEQ ID NO:2, the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:3, or the amino acid sequence of SEQ ID NO:5. The structures of the nucleic acid sequences are not properly described in the specification so as to allow one of ordinary skill in the art to envision all the members of the claimed genus. In order for one to be enable

to use the method throughout the full scope of the claims the target sequence must be clearly disclosed so that both antisense and ribozyme compounds may be properly designed.

In addition, it is well established in the art that there is a significant level of unpredictability regarding the behavior of antisense base therapeutics. According to Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also describes several "non-antisense effects", for example phosphorothioate modified oligonucleotides tend to bind to many proteins, protein binding in general by oligonucleotides may influence cell uptake, distribution, metabolism and excretion. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable, and thus much experimentation is required to screen multiple antisense compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Branch (1998) also teach that "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes to their specified target *in vivo* is unpredictable, the internal structures of the targeted mRNA molecules and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Antisense therapy is a highly unpredictable field and the skill in the art is high.

Both Branch and Crooke teach that the behavior of antisense/ribozyme based pharmaceuticals are unpredictable, therefore claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, the specification as filed does not describe the method for modulating the TRAF2 modulated/mediated effect comprising the use of antisense or ribozyme compounds or the pharmaceutical compositions comprising antisense oligonucleotides in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the lack of description regarding the target sequences, the known unpredictability regarding the behavior of antisense compounds *in vivo* and further with the production of the desired secondary effects, such as specifically modulating the expression of a particular gene, and the lack of guidance provided in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining the structures of the mRNA targets, the structures of the antisense oligonucleotides and ribozymes used in the recited methods, determining modes of delivery in a cell such that the processing of said mRNA target is modulated and the desired secondary effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

11. Claims 30-39 and 40-42 read on pharmaceutical compositions and methods for the prevention or treatment of a pathological condition associated with NF-kB induction or with any other activity mediated by TRAF2 or by other molecules to which a polypeptide according to claim 51 binds, said method comprising administering to a patient in need an effective amount of a polypeptide according to claim 51. In regards to the recited methods, the specification as filed does not disclose how the claimed compositions are to be used in order to prevent or treat a pathological condition associated with NF-kB induction or with any other activity mediated by TRAF2 or by other molecules to which a polypeptide according to claim 51 binds. It is not clear from the specification, that in order for prevention of the recited pathological conditions, whether the patient is potentially prone for such conditions or whether a recurrence is being prevented. It is also unclear as to whether the therapy to prevent recited here started months ahead or days ahead of a probable expectation of such pathological conditions? Is there a particular amount of the formulation that needs to be

administered? Is a particular treatment regimen necessary? Futhermore it is also unclear as to how long must such a treatment continue in order to prevent such pathological conditions? Applicant has only shown that one of skill in the art would expect the incidence of a pathological condition associated with NF-kB induction to be reduced, not completely prevented.

The claimed methods also read on gene therapy wherein a DNA molecule coding a polypeptide according to claim 51 is administered to a patient in order to prevent or treat a pathological condition associated with NF-kB induction. According to Anderson (1998), " Gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease. Several major deficiencies still exist including poor delivery systems, both viral and no-viral, and poor gene expression after genes are delivered." Orkin et al. (1995) state that " Daunting hurdles must be overcome if gene correction strategies are to achieve a meaningful clinical outcome.....Although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans." In addition, **In re Wands**, 858 F.d. 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations in determining whether or not undue experimentation would be involved in practicing inventions. These factors are: the quantity of experimentation necessary, the amount of direction or guidance needed, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims. The amount of experimentation necessary to determine the appropriate means to deliver the compositions to the correct tissues, and to determine a means to regulate the level of gene expression at the correct tissues at a sufficient level

to correct the condition to be treated or prevented, is beyond the scope of one with ordinary skill in the art.

In view of the lack of guidance provided in the specification of the instant application, the level of unpredictability in the art in regards to methods of prevention and gene therapy techniques, and the breadth of the given claims, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

April 21, 2000

REMY YUCEL, PH.D
PATENT EXAMINER